

Letters

Novel drug of choice in Eaton-Lambert syndrome

Sir: Muscle weakness in the myasthenic syndrome of Eaton-Lambert¹ is caused by diminished transmitter release from motor nerve endings² secondary to morphological destruction of the active release zones in the nerve terminals³ which is thought to have an autoimmune aetiology.^{4,5} Immunosuppressive therapy has recently been recommended⁶ but its full effect is delayed by several months and severe side effects may be expected during prolonged treatment. Symptomatic treatment with an immediately acting drug would be of value to the cancer patient with Eaton-Lambert syndrome, and if such a drug is proved safe it could also be used in the cryptogenic form of the disease. 4-aminopyridine has been tested,⁶⁻⁸ but its usefulness is limited by central nervous system stimulant effects sometimes causing seizures. We have tried another aminopyridine, 3,4-diaminopyridine (3,4-DAP), in three patients with Eaton-Lambert syndrome. This drug is known from animal experiments to be more potent in improving neuromuscular transmission⁹ and less convulsant¹⁰ than 4-aminopyridine.

Our first patient was a 70-year-old woman with cryptogenic Eaton-Lambert syndrome with marked difficulties in walking, pronounced dysarthria, ptosis, difficulty in swallowing, and constipation and inability to urinate. She further deteriorated and required mechanical respiratory assistance because of respiratory muscle weakness. The intravenous injection through a central venous cannula of 8 mg 3,4-DAP within 5 minutes caused marked improvement. The patient was able to breathe without respiratory assistance, ptosis disappeared, facial expression reappeared and muscle strength in arms and legs improved a lot. Examination of neuromuscular transmission by repetitive nerve stimulation showed marked decrease of the neuromuscular block. The i.v. injection caused much salivation and secretion from the respiratory tract, which was blocked by atropine intravenously. Treatment with repeated intravenous infusions of 3,4-DAP gave satisfactory clinical and electrophysiological improvement (fig). She received daily intravenous infusions of 6-9 mg 3,4-DAP 4 times a day with 0.5 mg atropine for 5 months without side effects. During this treatment she could breathe

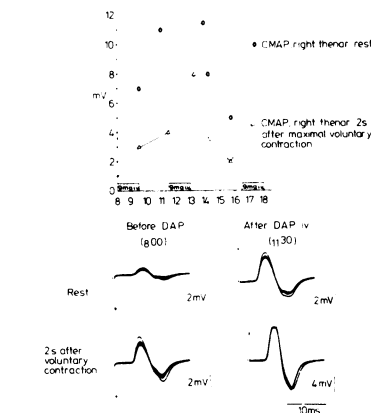


Fig Augmentation of the compound muscle action potential (CMAP) of the right thenar muscles at supramaximal stimulation of the median nerve after intravenous infusion of 3,4-diaminopyridine (DAP). The CMAPs at rest and 2 s after maximal voluntary contraction are illustrated and plotted in the diagram. Note different amplification of the lower right record.

without a respirator, walk with a stick, swallow normally and her urethral catheter could be removed. Oral administration of 3,4-DAP was also effective and later she was treated by 24 mg orally 4 times a day with equally good results. Interestingly, previous attempt to treat this patient with 4-aminopyridine had caused a fit.

Our second patient also had cryptogenic Eaton-Lambert syndrome. A 72-year-old woman with proximal muscle weakness and slight cranial nerve muscle symptoms clinically and electrophysiologically deteriorated in 1982. Her ability to walk decreased from 1000 to 200 m and she could no longer climb the stairs to her apartment. Intravenous injection of 8 mg, 3,4-DAP and oral administration of 30 mg markedly improved all muscle functions tested. Electrophysiological examination demonstrated maximum effect 1½ h after an oral dose and disappearance of effect about 2 h later. Continuous oral treatment with 18 mg 4 times a day drastically changed daily life of this patient from being a cripple to that of an almost normal retired lady being able to walk more than 1000 m and climb stairs. She has now been treated with this dose for three months without side effects except temporary perioral paraesthesias and transitory pain in her arm after i.v. injection.

Our third patient with Eaton-Lambert

syndrome was a 62-year-old woman with cancer of the gallbladder with metastasis to the liver. She had marked proximal muscle weakness with inability to walk, dysarthria and dysphagia. An i.v. infusion of 8 mg 3,4-DAP or 24 mg orally markedly improved muscle function and she could walk with minor support and her speech improved. Treatment with 24 mg 3,4-DAP orally 4 times a day was effective but after a short time interrupted by her death caused by pulmonary embolism.

From our results we conclude that 3,4-DAP is a highly potent and probably safe drug in Eaton-Lambert syndrome. Although only symptomatic treatment we suggest it is the present drug of choice in Eaton-Lambert syndrome associated with malignancy. Until the aetiology of the disease has been established and a safe long-term treatment delineated, 3,4-DAP may also be considered the first drug in the more rare cryptogenic form of the disease.

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Sustained levodopa therapy in tardive dyskinesia

Sir: The pathophysiology of tardive dyskinesias is still poorly understood, but striatal post-synaptic dopamine receptor hypersensitivity may be implicated.¹ Permanent discontinuation of the offending neuroleptic offers the best hope of relief, but the patients' mental state often precludes this. Tetrabenazine is the most effective drug treatment, but side-effects including sedation, depression, Parkinson's syndrome and akathisia are common. The longterm administration of levodopa to rodents has recently been shown to attenuate the behavioural and biochemical features of dopaminergic hypersensitivity.^{2,3} Promising results have also been reported in tardive dyskinesia giving sustained levodopa treatment² or small doses of dopamine receptor agonists.⁴ In view of these findings we have been encouraged to extend this approach to the treatment of patients with irreversible, persistent dyskinesias no longer receiving neuroleptics.

Seven patients (six female, one male) with moderate or severe tardive dyskinesia agreed to participate. Their mean age was 69 years (range 53-93) and the mean duration of involuntary movements was 7 years (range 3-12). Neuroleptics had been given for a mean period of 9.2 years (range 3-30) for schizophrenia, save for three with chronic dyspepsia, agoraphobia and depression respectively. Their conditions were static and their movement disorders comprised a bucco-linguo-masticatory syndrome in seven, additional limb chorea in five and torticollis in one. Two had co-existent akathisia, but none had Parkin-

son's disease. With one exception all had discontinued neuroleptics for at least one year (mean 4 yr) before the trial. Baseline clinical assessments were made by two independent observers using the AIM scale⁵ and dyskinesia was recorded simultaneously on video tape. Levodopa 300 mg daily in combination with benserazide was then gradually introduced (Madopar 125, 1 capsule 8 hourly) and the patients assessed at 14 day intervals by the same observers. After a minimum of 12 weeks sustained therapy, patients were re-filmed and the levodopa then discontinued abruptly. Follow-up observation continued for six months with AIM scale scoring.

An initial aggravation of the dyskinesias was seen in one patient following levodopa introduction, but otherwise no significant changes in dyskinesia severity occurred at any stage of the trial.

These disappointing results do not compare favourably with those obtained by Bjørndal and colleagues who reported modest improvement in drug-free patients following one month's levodopa therapy.⁶ Benefit has also been claimed with chronic levodopa in patients still receiving neuroleptics⁷ or in those who have just stopped them.⁸ Casey *et al.*⁹ however, using very large doses of levodopa in combination with benserazide for treatment periods of 8 weeks failed to produce benefit in five neuroleptic treated schizophrenics with tardive dyskinesia. In contrast to other studies we also failed to demonstrate an initial increase in dyskinesia following levodopa introduction.⁷ Further studies using dopamine receptor agonists and large doses of levodopa in this refractory group of incapacities are now under way.

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Giant aneurysm of the petrous portion of the carotid artery

Sir: Aneurysms of the internal carotid artery extracranially are rare; those arising from the petrous segment are particularly unusual. A survey of the literature showed approximately 30 reported cases.¹⁻¹⁹

A 28-year-old woman had been complaining of severe left ear pain, tinnitus and hearing loss for approximately six months. The pain was continuous and irradiated towards the face, the retromastoid region and sometimes down to her neck. At ENT consultation a vascular mass was found in the left middle ear. An attempted biopsy resulted in massive bleeding controlled by packing the ear. She was then referred to the neurosurgical department with the diagnosis of glomus tumour. Besides a left sensorineural deafness, neurological examination was normal. Both carotid pulses normally and no bruit was heard about the head and neck. Skull radiographs demonstrated a large area of bone erosion in the left petrous pyramid extending anteriorly into the sphenoid sinus. A sclerotic ring could be noticed around the lytic lesion, suggesting a chronic process. Left carotid arteriography revealed a large (1.5 × 2.5 × 5 cm.) aneurysm located in the petrous segment of the carotid artery projecting laterally into the middle ear, with normal intracranial arborisation. Right carotid arteriography with left carotid compression showed excellent cross filling of the left anterior cerebral and middle cerebral arteries, without aneurysm opacification.